17. (twice amended) An apparatus for introducing a therapeutic agent in a composition into at least one cell in a vessel in a subject, comprising:

a catheter having at least one inflatable balloon portion at a position other than the distal end of the catheter;

proximal to the at least one inflatable balloon portion, at least one infusion opening for introducing a composition containing a therapeutic agent into a vessel in a subject;

a first electrode positioned adjacent to an infusion opening; and

a second electrode proximal to and spaced from the first electrode a distance suitable for electroporating a therapeutic agent into a cell of a vessel of a subject into which the catheter is introduced.

REMARKS

Claims 1-28 are currently pending. The amendments above are being made to advance prosecution and, if necessary, to place the claims in better condition for appeal. As will be appreciated, the amendments to claims 1, 10, and 17 above serve to clarify the structure of Applicants' invention by removing extraneous "statement of use" language that does not impact the patentability of the claimed devices. These amendments do not expand the scope of the claimed invention, add no new matter, and are fully supported by the specification and claims as originally filed. None of these amendments is being made for reasons of patentability; instead, they simply clarify the subject matter Applicants' regard as their invention. For these reasons, Applicants respectfully submit that entry of the foregoing amendments at this stage is proper. That being said, Applicants reserve the right to later prosecute claims equivalent to or more broad than the claims as they existed prior to the entry of the foregoing amendment in this or a related

application.

Specifically, claims 1, 10, and 17 have been amended to clarify that the first and second electrodes are spaced on the catheter in such a way as to impart electroporation capability upon insertion of the catheter into a vessel of a patient. By spacing the electrodes an appropriate distance, it is possible to generate electric fields sufficient to enable a therapeutic agent to be electroporated into living cells in or of the vessel in a manner that does adversely affect cell

viability in and of itself. Applicants respectfully submit that such devices are both novel and non-obvious. For this reason, Applicants respectfully request reconsideration of the claims as amended in view of the following remarks.

a. 35 USC 103 (a) rejection in view of U.S. patent no. 5,505,700.

Claims 1-5, 7-14, 16-21, and 23-28 stand finally rejected under 103 (a) as allegedly being obvious over Leone, et al., U.S. patent no. 5,505,700. The Office Action states that the Leone, et al. patent discloses the invention substantially as claimed.

To the extent that this rejection could be held to apply to the claims as amended, Applicants respectfully traverse. In order to establish a prima facie case of obviousness in view of a single reference, as here, the burden is on the PTO to provide an explanation of why one of ordinary skill in the art at the time the invention was made would have been motivated to make the proposed modifications. There must also be a reasonable expectation of success. Finally, the cited reference must teach or suggest all the claim limitations. In this case, Applicants respectfully contend that none of these requirements has been met.

The Office Action asserts that the Leone, et al. patent discloses a catheter having at least one inflatable balloon portion, at least one infusion opening, and a first and second electrode, wherein the electrodes are positioned in such a way that when an impulse is applied an electric field sufficient to cause electroporation is achieved. Applicants respectfully disagree.

The Leone, et al. patent in fact discloses a catheter for delivering a charged treatment fluid (or charged components, e.g., a drug, thereof) to a patient by using electrodes on the catheter to force the treatment fluid (or its components) out of the catheter. See, for example, the abstract of the Leone, et al. patent. The technical advance set forth in the Leone, et al. patent was the use of a catheter that itself included both "internal" and "integral" electrodes, in contrast to previously known devices, which contained only one of the two electrodes needed to generate the electric field needed to drive the treatment fluid from the catheter. In earlier devices, the other electrode needed to complete the circuit purportedly was placed externally on the patient. See, for example, column 1, line 52, through column 2, line 53, of the Leone, et al. patent.

It is also important to note that while the Leone, et al. patent makes passing reference to "electroporation", it does so in a context different from that of the instant invention.

Specifically, at column 7, lines 39-44, the Leone, et al. patent states, "The invention can also be used to effect drug release by electroporation, which is the electrical breakdown of cells which contain substances such as hemolytic compounds, genes, and the like." (emphasis added) Applicants respectfully submit that the "electrical breakdown of cells" to release agents contained therein to effect treatment, as briefly discussed in the Leone, et al. patent, is distinctly different from the process made possible by Applicants' device. Specifically, as described at page 1, lines 11-15, of their specification, Applicants define electroporation as the use of electric fields to create pores in cells, without permanent damage, in order to incorporate compounds into live cells.

As emphasized in the amended claims, above, the spacing between the first and second electrodes is important in order to provide true "electroporation" capability. As described at page 1, lines 16-22, of the instant specification, creating an electric field of the desired strength at the desired site is important in order to minimize cell damage attributable to the electroporation process. As explained by Applicants, electric field strength ("E", measured, for example, in terms of volts/cm) can be determined by the formula E=V/d, where "V" equals the voltage (measured in volts) and "d" is the distance (measured, for example, in centimeters) between the electrodes. As claimed after entry of the amendment above, any spacing suitable to deliver the desired electric field can be employed.

Because the problems sought to be solved by the Leone, et al. patent, namely the use of an electrode attached to a patient's skin and the consequent "undesirable aspects of having to pass the electric current [for iontophoresis] through body tissue," are completely different than that addressed by Applicants' invention (i.e., how to effect delivery of therapeutic agents into living cells inside a vessel in a subject by using a catheter having electrodes appropriately spaced to generate an electric field sufficient to create pores in but minimize damage to living cells such that the desired therapeutic agent can enter the cells to exert a therapeutic effect), Applicants submit that the ordinarily skilled artisan would not have been motivated to alter the device disclosed in the Leone, et al. patent in order to space the electrodes to provide an electroporating electric field. This difference, electrodes to generate a field useful for merely drawing a charged treatment fluid (or its charged constituents) through a vessel after being expelled from a catheter disposed therein, as compared to electrodes spaced so as to all a pulsed electric field to be generated that is adequate to open pores in living cells with minimal damage, is key. It is also

worth noting in the device of the Leone, et al. patent, the charge of the treatment fluid (or the desired component thereof) dictates the polarity of the electrodes of the device, as the "electrical circuit influences the path of travel of the medicament to direct same toward the area being treated". Leone, et al. patent, column 2, lines 51-53. This concept is further discussed at column 4, lines 49-57, where it is stated in reference to Figure 2 of the patent that:

> "Movement of the medicament to the vessel wall 32 and any diseased area 33 thereon is enhanced by operation of the electrodes and their associated electrical source15. After the medicament is infused either out of the port(s) 19 or through pores or osmotic passageways of catheter treatment length 34, a voltage is applied such that ionically charged medicament fluid forces the fluid to move away from a like-charged internal electrode component 35 and toward the vessel wall. The charge associated with the internal electrode 35 is developed by a voltage drop between internal electrode 35 and one or more integral electrode(s) 36. Internal electrode 35 and integral electrode(s) 36 are connected to opposite poles of the electrical or EMF source through suitable wires...". Id.

As the ordinarily skilled artisan would appreciate, according to the Leone, et al. patent, for an electrically charged medicament or component thereof, the electrode(s) (i.e., the "internal electrodes") nearest the port(s) where the medicament or component leaves the catheter must be of like charge, with the other (i.e., "integral") electrode(s) having the opposite charge. The combination of electrostatic repulsion and attraction serves to move the medicament or component through the vessel lumen after it is expelled from the catheter. It must also be noted that if an active ingredient is not charged, a charged fluid is essential for the device of the Leone, et al. patent to operate. On the other hand, the electrical charge of the fluid (or components carried therein) infused through Applicants' catheters is not important to the ultimate function of the device, as the electric field created by Applicants' invention is used to open pores in living cells, not to induce fluid (or components carried therein) to move in one direction or another. Moreover, there is nothing to suggest that modification of the device disclosed in the Leone, et al. patent would reasonably have been expected to result in a device useful for electroporation in the context described by Applicants, i.e., the minimally or non-damaging use of electric fields to open pores in living cells in order to allow compounds to enter the cells and effect therapy. Lastly, because the Leone, et al. patent neither suggests modification of the device disclosed therein as suggested in the Office Action nor provides a reasonable expectation of success, no

prima facie case of obviousness can, in fact, be established in view of this reference in the context of the instant claims. For this reason, Applicants respectfully submit that this 35 U.S.C. § 103 rejection should be withdrawn.

b. 35 USC 103 (a) rejection in view of U.S. patent nos. 5,505,700 and 5,634,899.

Claims 6, 15, and 22 are rejected under 103 (a) as allegedly being obvious over the Leone, et al., patent in view of the Shapland, et al. patent (USP 5,634,899). Herein, Applicants have canceled claims 6, 15, and 22 to advance prosecution, thereby obviating the basis of this rejection. Accordingly, Applicants respectfully submit that this rejection should also be withdrawn.

CONCLUSION

Applicants respectfully submit that upon entry of the amendment above, the remaining claims will be in condition for allowance. Applicants therefore earnestly solicit a notice indicating such. Should any issues or questions remain, to avoid the preparation of an additional official action and response thereto, the Examiner is encouraged to telephone the undersigned at 858.350.9690 so that the same may be promptly resolved.

Respectfully submitted,

Dated: 25 April 2003

By:
Daniel M. Chambers
Biotechnology Law Group
Attorney for Applicants
Reg. No. 34,561

MARKED UP VERSION

1. (thrice amended) An apparatus for introducing a therapeutic agent in a composition into at least one cell in a vessel in a subject, comprising:

a catheter having at least one inflatable balloon portion;

proximal to the at least one inflatable balloon portion, at least one infusion opening in the catheter for introducing [the] a composition containing a therapeutic agent into a vessel in [into the] a subject [proximal to the at least one inflatable balloon portion];

a first electrode on the catheter positioned adjacent to [at least one] an infusion opening; and

a second electrode on the catheter proximal to but spaced from the first electrode a distance suitable for electroporating a therapeutic agent into a cell in the vessel of the subject into which the catheter is introduced[, wherein said first and second electrodes are suitable to receive an electric pulse having an electroporating voltage in the range of about 10 Volts to 200 Volts and having a pulse length of about 100 microseconds to 100 milliseconds, and wherein said second electrode is proximally positioned with respect to the first electrode and the subject such that when the electric pulse is applied to the first and second electrodes an electric field is generated in the subject of between 0.5 and 5.0 kV/cm, which is sufficient to cause electroporation of at least one cell in the vessel before, during or after introduction of the composition into the subject through the at least one infusion opening].

10. (twice amended) A catheter, comprising:

a first inflatable balloon portion near a [the] distal end of the catheter;

a second inflatable balloon portion proximal to the first inflatable balloon portion such that upon inflation of the first and second balloon portions in a vessel in a subject the vessel is occluded, [wherein inflation of the first and second balloon portions occludes a vessel between the first and second balloon portions];

[at least one] an infusion opening for introducing a composition containing a therapeutic agent into [a] the subject, wherein the infusion opening is located between the first and second balloon portions;

a first electrode positioned adjacent to or integral with the [at least one] infusion opening; and

a second electrode proximal to and spaced from the first electrode a distance suitable for electroporating a therapeutic agent into a cell in a vessel of a subject into which the catheter is introduced[, wherein said first and second electrodes are suitable to receive an electric pulse having an electroporating voltage in the range of about 10 Volts to 200 Volts and having a pulse length of about 100 microseconds to 100 milliseconds, and wherein said second electrode is proximally positioned with respect to the first electrode and the subject such that when the electric pulse is applied to the first and second electrodes an electric field is generated in the subject of between 0.5 and 5.0 kV/cm, which is sufficient to cause electroporation of at least one cell in the vessel before, during or after introduction of the composition into the subject through the at least one infusion opening].

17. (twice amended) An apparatus for introducing a therapeutic agent in a composition into at least one cell in a vessel in a subject, comprising:

a catheter having at least one inflatable balloon portion at a position other than the distal end of the catheter;

proximal to the at least one inflatable balloon portion, at least one infusion opening for introducing a [the] composition containing a therapeutic agent into a vessel in a [the] subject;

a first electrode positioned adjacent to an [at least one] infusion opening; and

a second electrode proximal to and spaced from the first electrode a distance suitable for electroporating a therapeutic agent into a cell of a vessel of a subject into which the catheter is introduced [, wherein said first and second electrodes are suitable to receive an electric pulse having an electroporating voltage in the range of about 10 Volts to 200 Volts and having a pulse length of about 100 microseconds to 100 milliseconds, and wherein said second electrode is proximally positioned with respect to the first electrode and the subject such that when the electric pulse is applied to the first and second electrodes an electric field is generated in the subject of between 0.5 and 5.0 kV/cm, which is sufficient to cause electroporation of at least one cell in the vessel before, during or after introduction of the composition into the subject through the at least one infusion opening].